

REMARKS

Claims 30-34, 36-44, 47-52 and 54-57 are pending in the above-identified application.

Unity of Invention

Applicant respectfully maintains a traversal of the Unity of Invention Requirement for the reasons stated in the Response filed December 15, 2010. It is also submitted that there does not appear to be a significant burden placed on the Examiner to examine all the claims because of the significant overlap with respect to search and examination issues among the groups. The sulfone adduct III or sulfone adducts IV appear in all claims of the present application. The sulfone adducts III and IV are of such structurally distinct character that a search for these structures ought not to cause any significant burden on the Examiner. Thus, it is again respectfully requested that the Unity Requirement be withdrawn.

Issues under 35 USC 103(a)

Claims 30-34, 36-43 and 48-50 have been rejected under 35 USC 103(a) as being unpatentable over Calverley (Tetrahedron, vol. 43, no. 20, pp. 4609-4619, (1987)).

This rejection is traversed based on the following reasons

It is the Examiner's position that the claims are obvious, since uses of a sulfone adduct in the preparation of calcipotriol would have been obvious in view of Calverley. However, the sulfone adducts of Calverley have chemical structures significantly different from the sulfone adducts employed in the present invention. Furthermore, the sulfone adducts of Calverley are used at different stages in an overall different synthetic pathway so as to serve different purposes, as compared to the present invention. Therefore, the results obtained in the method of the present invention using different sulfone adducts cannot be considered obvious.

Calverley describes the preparation of calcipotriol in which a specific sulfone adduct (**6a,6b**) serves as an intermediate to obtain the desired configuration at C-5, the (5E)-vitamin derivative **8**, by cheletropic extrusion of SO₂ (Page 4610, 3rd paragraph), or the specific sulfone adduct (**13a, 13b**) serves to protect the triene system as a dienophile adduct during ozonolysis of the double bond at C-22 to give the aldehyde (**14a, 14b**) (page 4611, 2nd paragraph).

Calverley describes the reduction of the C-24 ketone on the *unprotected triene-system* (not a sulfone adduct), without a chiral auxiliary present, leading to formation of an excess of the *undesired* epimer (compound **21** (24-R)) compared to the desired epimer (compound **22** (24-S)) (ratio **21** : **22** 61:38; isolated yield **21** : **22** 55% : 33%).

The Examiner states that Calverley teaches reduction of a sulfone adduct. Taking into account the above explanation, Applicant respectfully disagrees with this statement, as well as the conclusion by the Examiner that that the invention is obvious.

The present invention claims a method of obtaining an *enrichment of the desired diastereomer IVa (24-S)* compared to the undesired diastereomer IVb (24-R) during the reduction of the C-24 ketone in the presence of a chiral auxiliary. That is, the present invention is directed to a *diastereoselective reduction*. On the other hand, Calverley reports reduction of the C-24 ketone without the presence of a chiral auxiliary in which an excess of the *undesired* diastereomer was obtained. In the present invention it has surprisingly been found that protecting the triene system as a sulfone adduct prior to reduction of the C-24 carbonyl group in the presence of chiral auxiliaries affords an *enrichment of the desired diastereomer IVa (24-S)* compared to undesired diastereomer IVb (24-R). Thus, the use of the sulfone adduct in the present invention serves to facilitate the formation of the desired epimer at C-24 as well as to protect the triene system during the reduction of the carbonyl at C-24 in the presence of a chiral auxiliary, whereas the sulfone adducts in Calverley solely serve to direct the formation of the desired configuration at C-5 during cheletropic extrusion of SO₂; or to protect the triene system during ozonolysis of the double bond at C-22. The *reversal of enrichment* to obtain an excess of the desired epimer (24-S) compared to the undesired epimer (24-R) using the sulfone adduct III as an intermediate in combination with chiral auxiliaries according to the presently claimed invention could therefore not have been predicted from prior art; and the *reversal of enrichment* to obtain an excess of the desired epimer (24-S) is thus completely unexpected.

The present application discloses various reaction conditions for reducing the C-24 ketone to C-24 alcohol, all leading to enrichment of the *desired* diastereomer IVa (24-S) in various ratios compared to diastereomer IVb (24-R). In example 9, the ratio IVa:IVb (24-S : 24-R) lies between 72-78:22-28. In example 16 the compound IV is deprotected to V, here the ratio Va:Vb (24-S : 24-R) varies from 56:44 to 76:24 depending on the reaction conditions and the reagents of the reduction. The examples illustrate that the invention has led to a substantial

improvement of the synthesis of calcipotriol compared to the ratios obtained in Calverley wherein the undesired epimer (24-R) is obtained in excess (24-S : 24-R 38 : 61, Tetrahedron, Vol. 43, 20, 4609-4619). Vitamin D2 which is used as starting material for the present preparation of calcipotriol is very costly and therefore the substantial enrichment of a desired diastereomer as discussed above is a critical invention for a more cost-effective preparation of calcipotriol on an industrial scale. Calverley not only fails to suggest the method of the present invention, but also fails to recognize the advantages discussed above. Consequently, significant patentable distinctions exist over Calverley, such that the above rejection must be withdrawn.

It is submitted for the reasons above that the present claims define patentable subject matter such that this application should now be placed in condition for allowance.

If any questions arise in the above matters, please contact Applicant's representative, Andrew D. Meikle (Reg. No. 32,868), in the Washington Metropolitan Area at the phone number listed below.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

By 

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